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ST. JUDE CHILDREN'S RESEARCH HOSPITAL			STEADMAN, DAVID J	
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332 N. LAUDERDALE			ART UNIT	PAPER NUMBER
MEMPHIS, TN 38105			1656	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>
	10/078,927	CURRAN ET AL.
	<b>Examiner</b>	<b>Art Unit</b>
	David J. Steadman	1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 18 January 2007 and 21 May 2007.  
 2a) This action is FINAL.                            2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 1,4-8,10,11,13-15,32 and 35-40 is/are pending in the application.  
 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 1,4-8,10,11,13-15,32 and 35-40 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)	5) <input type="checkbox"/> Notice of Informal Patent Application
Paper No(s)/Mail Date _____	6) <input type="checkbox"/> Other: _____

**DETAILED ACTION*****Status of the Application***

[1] A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114.

Applicant's submissions filed on 1/18/07 and 5/21/07 has been entered.

[2] Claims 1, 4-8, 10-11, 13-15, 32, and 35-40 are pending in the application.

[3] Applicant's amendment to the claims in the Appeal Brief filed on 1/18/07 is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[4] Applicant's arguments filed on 1/18/07 in response to the Office action mailed on 5/1/06 are acknowledged. Applicant's arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[5] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

***Specification/Informalities***

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[6] The objection to the specification as introducing new matter by way of the specification amendments filed on 4/25/2005 and 11/21/2005 is maintained for the reasons of record and the reasons stated below. The objection was fully explained in a prior Office action.

**RESPONSE TO ARGUMENT:** Applicant argues (beginning at p. 15 of the Appeal Brief filed on 1/18/07) 37 CFR 1.57, which is used to support the objection, was added only on September 21, 2004, became effective on October 21, 2004, and that MPEP 608.01(p) was not amended until October 21, 2004, where both occurrences were well after the instant application's filing date of February 19, 2002. Applicant further argues that even if held to the standard of 37 CFR 1.57, 37 CFR 1.57(g)(1) allows for correction to comply with 37 CFR 1.57(b)(1) if the application conveys an intent to incorporate the material by reference. According to applicant, because the specification discloses that the Dab1 proteins are defined as including proteins cloned from GenBank Accession numbers 328851 and 1771281, this is an indication of intent for these publications to be incorporated by reference.

Applicant's argument is not found persuasive. The examiner acknowledges citation of GenBank Accession Numbers 3288851 and 1771281 in the specification at p. 4, lines 24-25. However, according to MPEP § 608.01(p), incorporation by reference of material in a non-patent document "must be set forth in the specification and must: (1) Express a clear intent to incorporate by reference by using the root words "incorporat(e)" and "reference" (e.g., "incorporate by reference"); and (2) Clearly identify the referenced patent,

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application, or publication." See 37 § 1.57(b). MPEP § 608.01(p) further states, "[i]f a reference to a document does not clearly indicate an intended incorporation by reference, examination will proceed as if no incorporation by reference statement has been made and the Office will not expend resources trying to determine if an incorporation by reference was intended."

It is noted that there is no clear intent to incorporate by reference the sequences of GenBank Accession Numbers 3288851 and 1771281 using the root words "incorporat(e)" and "reference" (e.g., "incorporate by reference"), which is undisputed by applicant. Thus, according to MPEP § 608.01(p), "examination will proceed as if no incorporation by reference statement has been made." As such, the examiner considers the sequences of SEQ ID NO:4 and 5 to be new matter.

While applicant argues that 37 CFR 1.57 and MPEP 608.01(p) do not apply to this application by virtue of the application being filed prior to the effective date of 37 CFR 1.57 and the date of amendment of MPEP 608.01(p), the examiner can find no provision that excludes applications having a filing date of the instant application from being subject to 37 CFR 1.57 and MPEP 608.01(p) and applicant has presented no evidence of such. Thus, it is the examiner's position that the instant application is subject to the provisions of 37 CFR 1.57 and MPEP 608.01(p).

Further, it is noted that 37 CFR 1.57(g)(1) and (2) would not appear to apply in this case. 37 CFR 1.57(g)(1) states, "[a] correction to comply with paragraph (b)(1) of this section is permitted *only if the application as filed clearly*

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*conveys an intent to incorporate the material by reference*" (emphasis added). According to 37 CFR 1.57(b)(1), it appears that an application clearly conveys an intent to incorporate material "by using the root words 'incorporat(e)' and 'reference' (e.g., 'incorporate by reference')." As noted above and undisputed by applicant, the root words "incorporate" and "reference" do not appear to be used in association with the disclosed GenBank Accession Numbers. While the examiner acknowledges citation of GenBank Accession Numbers 3288851 and 1771281 in the specification at p. 4, lines 24-25, this appears to be "mere reference to material," which, according to 37 CFR 1.57(g)(1), "does not convey an intent to incorporate the material by reference."

***Claim Rejections - 35 USC § 112, Second Paragraph***

[7] Claims 36-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] The term "candidate sequence preferred by cdk5 activity" in claims 36 (claim 37 dependent therefrom) and 38-40 is a relative term which renders the claims indefinite. The term "candidate sequence preferred by cdk5 activity" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. While it is acknowledged the specification at p. 5, top, discloses, "'Candidate sequence' means a sequence of amino acids which contains a serine followed by a proline in +1 position and a

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lysine in +3 position, the serine being a preferred site for Cdk5 activity (Songyang et al., Mol Cell Biol, 16:6486-6493, 1996)," it is unclear as to the scope of those "candidate sequences" as defined in the specification that are "preferred" by Cdk5 over those that are not considered to be "preferred." It is suggested that applicant clarify the meaning of the noted term.

**RESPONSE TO ARGUMENT:** Beginning at the bottom of p. 10 of the Appeal Brief filed on 1/18/07, applicant notes the specification's definition of "candidate sequence" and further notes the reference of Songyang et al., which is asserted to teach a sequence "which contains a serine followed by a proline in +1 position and a lysine in +3 position" is the "distinct optimal peptide substrate for the Cdk5 kinase." According to applicant, serines 491 and 515 of murine Dab1 were predicted to be sites of Cdk5 phosphorylation, which was experimentally verified in this application. According to applicant, a skilled artisan would recognize the meaning of the term "Cdk5 serine kinase activity" and, because the specification identifies what is intended as being a "candidate sequence," would be able to identify those "candidate sequences" that are preferred by cdk5 activity.

Applicant's argument is not found persuasive. While the examiner acknowledges the specification's definition of "candidate sequence," as noted above, it is unclear from the specification and the claims as to which of those sequences encompassed by the definition are intended as being "preferred" over those that are not "preferred" by a "Cdk5" polypeptide, which is defined in the specification as encompassing any protein "with serine/threonine kinase activity

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that is structurally homologous to the mitotic cyclin dependent kinases.” Put another way, how does a skilled artisan distinguish those “preferred” candidate sequences as defined in the specification from those that are not?

[b] According to MPEP 2173.05(b), “[a] claim may be rendered indefinite by reference to an object that is variable.” Claim 39 is indefinite in the recitation of “GenBank accession number 1771281” as it is unclear as to the scope of sequences that are referenced by GenBank accession number 1771281. It is well-known to one of skill in the art that sequences disclosed in GenBank can be revised due to, e.g., identification of sequencing errors or identification of a previously unrecognized initiation methionine. Furthermore, it is noted that “GenBank accession number 1771281” indicates that the encoded polypeptide is “mDab555,” not a Dab1 protein as recited in the claims. As such, it is unclear as to the scope of polypeptides that are encompassed by the “amino acid sequence encoded by...GenBank accession number 1771281.”

**RESPONSE TO ARGUMENT:** Applicant argues (beginning at p. 12 of the Appeal Brief filed on 1/18/07) the USPTO has issued patents reciting a genbank accession number and there is no *per se* rule against the use of genbank accession numbers in claims. According to applicant, the use of “GenBank accession number 1771281” in the claim is clear and definite because a skilled artisan would recognize the relevant GenBank accession number 1771281 sequence at the time of the invention and any changes due to revision “would not be expected to change the characteristics of these proteins that are important in the context of the claimed invention.”

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Applicant's argument is not found persuasive. There is no dispute that US patents have issued that refer to sequences by a GenBank accession number, however, each application is examined on its own merits. Therefore, the examiner will focus on the facts of the instant application. It is the examiner's position that the facts of this case lead to the conclusion that the recitation of "GenBank accession number 1771281" is indefinite for reasons that follow.

In this regard, applicant appears to acknowledge that the GenBank accession number referenced in the claim has been revised and that future changes to the sequence "might be made" (Appeal Brief at p. 11, bottom). As such, it would appear that applicant acknowledges that the sequence of a GenBank Accession is variable. Because the sequence of a GenBank Accession is variable, it is unclear as to whether the polypeptide encoded by GenBank accession number 1771281 is limited to the polypeptide encoded by the nucleotide sequence of GenBank accession number 1771281 at the time of the invention, or whether the term is intended as encompassing future revised sequences. In view of applicant's argument, specifically that "any changes that might be made to the Cdk5 or Dab1 sequences would not be expected to change the characteristics of these proteins...", it would appear that applicant intends for the claim to encompass any polypeptides encoded by future revised sequences.

According to MPEP 2173, "[t]he primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent." Because the sequence of GenBank accession number 1771281 is

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variable and, based on applicant's remarks suggesting the claims encompass sequences with future revisions, it is unclear as to the scope of recited Dab1 proteins and thus, a skilled artisan would not be "informed of the boundaries of what constitutes infringement of the patent."

While applicant argues that "any changes that might be made to the Cdk5 or Dab1 sequences would not be expected to change the characteristics of these proteins...", this statement appears to be speculative, particularly as applicant has provided no objective evidence to support this allegation. According to MPEP 716.01(c), "[t]he arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965)."

**[c]** Claim 37 is indefinite in the recitation of "reference to amino acid positions of SEQ ID NO:1" and "reference to amino acid positions of SEQ ID NO:2." It is unclear as to what "positions" of SEQ ID NO:1 and/or 2 that are intended as being encompassed by the claims. Does the term mean to be interpreted as requiring the full-length, i.e., all positions, of SEQ ID NO:1 and/or 2 or is the term meant to be interpreted as requiring a subset of positions of SEQ ID NO:1 and/or 2? It is suggested that applicant clarify the meaning of the noted phrase.

***Claim Rejections - 35 USC § 112, First Paragraph***

**[8]** The new matter rejection of claims 1, 4-8, 10-11, 13-15, 32, and 35 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action.

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**RESPONSE TO ARGUMENT:** Applicant argues (beginning at p. 15 of the Appeal Brief filed on 1/18/07) 37 CFR 1.57, which is used to support the rejection, was added only on September 21, 2004, became effective on October 21, 2004, and that MPEP 608.01(p) was not amended until October 21, 2004, where both occurrences were well after the instant application's filing date of February 19, 2002. Applicant further argues that even if held to the standard of 37 CFR 1.57, 37 CFR 1.57(g)(1) allows for correction to comply with 37 CFR 1.57(b)(1) if the application conveys an intent to incorporate the material by reference. According to applicant, because the specification discloses that the Dab1 proteins are defined as including proteins cloned from GenBank Accession numbers 328851 and 1771281, this is an intent for these publications to be incorporated by reference.

Applicant's argument is not found persuasive. The examiner acknowledges citation of GenBank Accession Numbers 3288851 and 1771281 in the specification at p. 4, lines 24-25 of the specification. However, according to MPEP § 608.01(p), incorporation by reference of material in a non-patent document "must be set forth in the specification and must: (1) Express a clear intent to incorporate by reference by using the root words "incorporat(e)" and "reference" (e.g., "incorporate by reference"); and (2) Clearly identify the referenced patent, application, or publication." See 37 § 1.57(b). MPEP § 608.01(p) further states, "[i]f a reference to a document does not clearly indicate an intended incorporation by reference, examination will proceed as if no incorporation by reference statement has been made and the Office will not

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expend resources trying to determine if an incorporation by reference was intended."

It is noted that there is no clear intent to incorporate by reference the sequences of GenBank Accession Numbers 3288851 and 1771281 using the root words "incorporat(e)" and "reference" (e.g., "incorporate by reference"). Thus, according to MPEP § 608.01(p), "examination will proceed as if no incorporation by reference statement has been made." As such, upon reconsideration of the incorporation of the sequences of GenBank Accession Numbers 3288851 and 1771281 into the specification, the examiner considers the sequences of SEQ ID NO:4 and 5 to be new matter.

While applicant argues that 37 CFR 1.57 and MPEP 608.01(p) do not apply to this application by virtue of the application being filed prior to the effective date of 37 CFR 1.57 and the date of amendment of MPEP 608.01(p), the examiner can find no provision that excludes applications having a filing date of the instant application from being subject to 37 CFR 1.57 and MPEP 608.01(p) and applicant has presented no evidence of such.

Further, it is noted that 37 CFR 1.57(g)(1) and (2) would not appear to apply in this case. 37 CFR 1.57(g)(1) states, "[a] correction to comply with paragraph (b)(1) of this section is permitted *only if the application as filed clearly conveys an intent to incorporate the material by reference*" (emphasis added). According to 37 CFR 1.57(b)(1), it appears that an application clearly conveys an intent to incorporate material "by using the root words 'incorporat(e)' and 'reference' (e.g., 'incorporate by reference')." As noted above and undisputed by

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applicant, the root words “incorporate” and “reference” do not appear to be used in association with the disclosed GenBank Accession Numbers. While the examiner acknowledges citation of GenBank Accession Numbers 3288851 and 1771281 in the specification at p. 4, lines 24-25, the is appears to be “mere reference to material,” which, according to 37 CFR 1.57(g)(1), “does not convey an intent to incorporate the material by reference.” As such, reference to the sequences of SEQ ID NO:4 and 5 in the claims is considered to be new matter.

[9] Claim 40 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

MPEP § 2163.II.A.3.(b) states, “when filing an amendment an applicant should show support in the original disclosure for new or amended claims” and “[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description.”

Claim 40 recites the limitation “Disabled 1 protein (Dab1) comprising SEQ ID NO:3.” The specification provides descriptive support for a broad genus of Dab1 polypeptides (specification at p. 4, lines 22-23) and further discloses

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specific species of such Dab1 polypeptides as those encoded by GenBank Accession Numbers (p. 4, lines 24-25). The scope of "Disabled 1 protein[s] (Dab1) comprising SEQ ID NO:3" is a subgenus of the broader genus of Dab1 proteins. According to MPEP 2163.05.II, whether a subgenus constitutes new matter "must be decided on its own facts in terms of what is reasonably communicated to those skilled in the art. *In re Wilder*, 736 F.2d 1516, 1520, 222 USPQ 369, 372 (Fed. Cir. 1984)."

Applicant points to the specification at p. 3, lines 25-29 and p. 15, lines 16-17 as showing support for the recited subgenus of Dab1 proteins. Page 3, lines 25-29 of the specification discloses, "SEQ ID NO:3 is the portion of the Dab1 protein used as the antigen for the generation of antibodies to phosphorylated serine 491. The first amino acid in this 14 amino acid peptide corresponds to threonine 484 of murine Dab 1. A phosphate group is linked to serine 491 of the antigen, which is an amino acid in Dab1 that is selectively phosphorylated by Cdk5," while the relevant portion of page 15, lines 16-17 of the specification discloses, "*Phosphopeptide antibodies. Synthesis of the phosphopeptide PSer491 (TPAPRQSS(PO4)PSKSSA) (SEQ ID NO:3).*" This disclosure appears to relate to the description of SEQ ID NO:3 as an antigen in the production of a phosphoantibody. Contrary to applicant's assertion, this disclosure does not appear to describe a subgenus of Dab1 proteins with a common structural feature of SEQ ID NO:3.

**RESPONSE TO ARGUMENT:** Applicant argues (beginning at the bottom of p. 13 of the Appeal Brief filed on 1/18/07) SEQ ID NO:3 is present in Dab1

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polypeptides from a variety of sources and is not present in proteins other than Dab1, even in closely related proteins. Applicant further argues the structural characteristic of SEQ ID NO:3 provides a distinguishing structural feature for the genus of recited Dab1 proteins and the use of this peptide as an antigen would indicate to a skilled artisan that this sequence is characteristic of Dab1 proteins and is useful for distinguishing Dab1 proteins from others.

Applicant's argument is not found persuasive. There is no dispute that SEQ ID NO:3 may be present in other naturally occurring Dab1 proteins or that the claim requires all members of the genus to have this common structural feature. What is at issue is whether or not the specification provides descriptive support for the claim 40 limitation of "Disabled 1 (Dab1) protein comprising SEQ ID NO:3." As noted by applicant, the specification characterizes SEQ ID NO:3 as a peptide used as an antigen in the production of a phosphoantibody. In this case, disclosure of SEQ ID NO:3 as peptide antigen for phosphoantibody production does not appear to provide descriptive support for a subgenus of Dab1 polypeptides requiring the common structural feature of SEQ ID NO:3.

[10] Claims 36-38 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

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According to MPEP 2163.II.A.1, in evaluating a claimed invention for adequate written description, the examiner should determine what the claim as a whole covers. "Claim construction is an essential part of the examination process. Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description. See, e.g., *In re Morris*, 127 F.3d 1048, 1053-54, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997)." Claims 36-37 and 40 are drawn to a method for detecting Cdk5 serine kinase activity in a sample by determining whether the C-terminal domain of a genus of Dab1 polypeptides is phosphorylated on a serine within a "candidate sequence preferred by cdk5 activity" (claim 36), optionally wherein the serine is selected from position 3 of SEQ ID NO:1, or position 21 of SEQ ID NO:2 (claim 37) or optionally wherein the C-terminal domain of Dab1 comprises SEQ ID NO:3 (claim 40). Claim 38 is drawn to a method for detecting Cdk5 serine kinase activity by immunoprecipitating a genus of Dab1 polypeptides. According to the specification, "Dab1" is defined as "an intracellular adapter protein that is phosphorylated by Cdk5 activity and by reelin tyrosine kinase activity" (specification at p. 4, lines 22-23). As such, claims 36-38 encompass the use of any polypeptide having any sequence of amino acids that is considered to be an "intracellular adapter protein" and that is phosphorylated by Cdk5 activity and by reelin tyrosine kinase activity. It is noted that there is no requirement that the genus of Dab1 proteins even have a serine residue and it is further noted that the limitations of claim 37 do not limit the structures of the genus of Dab1 polypeptides, only what is being detected by the claimed method. Claim 40

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requires that the genus of Dab1 proteins comprises SEQ ID NO:3 in its “carboxy terminal domain,” wherein SEQ ID NO:3 is a 14 amino acid peptide, and outside of SEQ ID NO:3, the structures of the genus of Dab1 polypeptides are completely undefined.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In this case, the specification discloses only two representative species of Dab1 polypeptides that have a disclosed relationship of having a structure that is able to detect the function of Cdk5 serine kinase activity, *i.e.*, human Dab1 having GenBank accession number 3288851 and mouse Dab1 having GenBank accession number 1771281. The specification fails to describe any additional representative species of the recited genus of Dab1 polypeptides, which, as noted above, encompasses any polypeptide having any sequence of amino acids

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that is considered to be an "intracellular adapter protein" and that is phosphorylated by Cdk5 activity and by reelin tyrosine kinase activity (claims 36-38) or any Dab1 protein as defined above, comprising SEQ ID NO:3. While it is acknowledged that the specification identifies the structures of SEQ ID NO:1 and SEQ ID NO:2 as being the target phosphorylation sites on Dab1 by Cdk5, it is noted that the genus of Dab1 polypeptides is not required to comprise SEQ ID NO:1 and/or 2 and further that the specification fails to disclose or provide guidance regarding those amino acids of any Dab1 polypeptide as encompassed by the claims that can be altered and still maintain the ability to be phosphorylated by Cdk5 serine kinase activity. Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 ("definition by function ... does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is"). While it is acknowledged that all members of the genus of Dab1 proteins of claim 40 are required to have the 14 amino acid peptide of SEQ ID NO:3, however, this structural feature does not "constitute a substantial portion of the genus" of Dab1 polypeptides as encompassed by the claims. See *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 In this case, the genus encompasses widely variant species of Dab1 proteins, encompassing any polypeptides having any structures as noted above. As such, the disclosure of the two representative species of Dab1 proteins is insufficient to be representative of the attributes and features of *all*

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species encompassed by the recited genus. Given the lack of description of a representative number of Dab1 polypeptides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

**RESPONSE TO ARGUMENT:** Beginning at p. 5 of the Appeal Brief filed on 1/18/07, applicant argues the term “Dab1” was art-recognized and the specification discloses specific examples of Dab1-encoding nucleic acids and thus an exhaustive description need not be required and is preferably omitted. According to applicant the novelty of this invention is the Cdk5-specific phosphorylation of Dab1, which is the basis for the claimed methods, not the Dab1 polypeptide itself. According to applicant, the facts of *Falkner* and *Capon* support applicant’s position.

Applicant’s argument is not found persuasive. Although applicant asserts the novelty of the invention is the identification of Dab1 as the specific substrate for Cdk5, and not the Dab1 polypeptide itself, it is noted that the Dab1 polypeptide is nonetheless an essential or critical feature of the claimed invention and according to MPEP 2163.I.A, “[t]he claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art.” It is the examiner’s position that, for reasons that follow, the genus of polypeptides encompassed by the term “Dab1” are not conventional or known to one of skill in the art. There is no

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dispute that the term “Dab1” was used in the prior art or that the specification discloses two GenBank Accession Numbers that refer to nucleic acid sequences encoding two species of Dab1 polypeptides. However, as noted above, MPEP 2163.II.A.1 directs the examiner to give claims their “broadest reasonable interpretation in light of and consistent with the written description” and according to MPEP 2111.01.IV, “[w]here an explicit definition is provided by the applicant for a term, that definition will control interpretation of the term as it is used in the claim. *Toro Co. v. White Consolidated Industries Inc.*, 199 F.3d 1295, 1301, 53 USPQ2d 1065, 1069 (Fed. Cir. 1999).” In this case, the specification defines “Dab1” as “an intracellular adapter protein that is phosphorylated by Cdk5 activity and by reelin tyrosine kinase activity” (specification at p. 4, lines 22-23). To limit the genus of Dab1 polypeptides to those representative species of the specification would “thereby narrow the scope of the claim by implicitly adding disclosed limitations which have no express basis in the claim” and thus would be an “impermissible importation of subject matter from the specification into the claim.” See particularly MPEP 2111. In this case, the genus encompasses species of Dab1 polypeptides that were not known or art-recognized at the time of the invention, including mutants and variants of Dab1 polypeptide and any other protein that is broadly encompassed by the specification’s definition of Dab1 including any “intracellular adapter protein that is phosphorylated by Cdk5 activity and by reelin tyrosine kinase activity.” In view of a broad interpretation of the claims in view of the specification’s definition of “Dab1,” it is the examiner’s

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position that the specification fails to adequately describe the claimed invention sufficient to show possession.

[11] Claims 1, 4-8, 10-11, 13-15, 32, and 35-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting Cdk5 serine kinase activity by contacting Cdk5 with the Dab1 of SEQ ID NO:4 or 5, determining whether serine at position 491 of SEQ ID NO:4 or 5 is or is not phosphorylated, wherein phosphorylation of serine at position 491 indicates Cdk5 activity, does not reasonably provide enablement for the broad scope of claimed methods. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

"The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows:

(A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence

of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

*The breadth of the claims:* According to MPEP 2164.04, “[b]efore any analysis of enablement can occur, it is necessary for the examiner to construe the claims...and explicitly set forth the scope of the claim when writing an Office action.” Also, MPEP 2164.08 states, “[w]hen analyzing the enabled scope of a claim, the teachings of the specification must not be ignored because claims are to be given their broadest reasonable interpretation that is consistent with the specification.”

The claims are drawn to methods of detecting Cdk5 serine kinase activity by determining whether Dab1 is or is not phosphorylated on a serine. According to the specification, “Cdk5” is defined as “a protein with serine/threonine kinase activity that is structurally homologous to the mitotic cyclin dependent kinases” (p. 4, lines 14-15). Regarding claims 36-37 and 40, as noted above, claims 36-38 encompass the use of any polypeptide having any sequence of amino acids that is considered to be an “intracellular adapter protein” and that is phosphorylated by Cdk5 activity and by reelin tyrosine kinase activity and claim 40 requires that the genus of Dab1 proteins comprises SEQ ID NO:3 in its “carboxy terminal domain,” wherein SEQ ID NO:3 is a 14 amino acid peptide, and outside of SEQ ID NO:3, the structures of the genus of Dab1 polypeptides are completely undefined.

The broad scope of claimed methods is not commensurate with the enablement provided by the disclosure with regard to the scope of Cdk5 and Dab1 polypeptides as encompassed by the claims. In this case the disclosure is limited to a method for detecting Cdk5 serine kinase activity by contacting Cdk5 with the Dab1 of SEQ ID NO:4 or 5, determining whether serine at position 491 of SEQ ID NO:4 or 5 is or is not phosphorylated, wherein phosphorylation of serine at position 491 indicates Cdk5 activity.

*The nature of the invention:* According to applicant's remarks in the Appeal brief filed on 1/18/07, the nature of the invention "is based on the discovery that Dab1 is specifically phosphorylated by Cdk5...a substrate which is selectively phosphorylated by Cdk5 had not heretofore been identified. The discovery that Dab1 is specifically phosphorylated on serine within a preferred candidate sequence by Cdk5 is the basis for the invention" (Appeal Brief filed on 1/18/07 at p. 7).

*The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art:* While applicant asserts Dab1 is specifically phosphorylated by Cdk5 (Appeal Brief at p. 7), post-filing evidence would suggest otherwise. For example, the reference of Ohshima et al. (*Brain Res.* 1140:84-95, 2007) teaches that Cdc2 is *at least* one other kinase that phosphorylates Dab1 on serine/threonine residues (e.g., p. 85, right column, top and p. 86, Figure 1B). It is noted that according to the reference of Takeo (*Int. J. Dev. Biol.* 38:185-191, 1994), Cdc2 is a mitotic serine/threonine kinase and would appear to be encompassed by the specification's definition of "Cdk5" as "a

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protein with serine/threonine kinase activity that is structurally homologous to the mitotic cyclin dependent kinases." Also, according to the reference of Patrick et al. (*J. Biol. Chem.* 273:24057-24064, 1998), "[t]he substrate specificity of the p35/Cdk5 kinase is similar to that of the Cdc2 and Cdk2 kinases, phosphorylating the K(S/T)PX(K/R) consensus sequence motif" p. 24057, column 2, middle). As such, a skilled artisan would recognize the high level of unpredictability that a Dab1 polypeptide – even those polypeptides of SEQ ID NO:4 and 5 – phosphorylated on any serine residue as encompassed by the claims is not necessarily indicative of Cdk5 serine kinase activity.

Regarding the scope of "Dab1" polypeptides used in the claimed methods, it is noted that since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. Even conservative substitutions can alter protein function as evidenced by MPEP 2144.08.II.A.4.(c), which states, "[t]he effect of a conservative substitution on protein function depends on the nature of the substitution and its location in the chain. Although at some locations a conservative substitution may be benign, in

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some proteins only one amino acid is allowed at a given position. For example, the gain or loss of even one methyl group can destabilize the structure if close packing is required in the interior of domains. James Darnell et al., Molecular Cell Biology 51 (2d ed. 1990)." As such, a skilled artisan would recognize the high level of unpredictability in altering the Dab1 of SEQ ID NO:4 or 5 with an expectation that the resulting polypeptide would maintain a conformation that is able maintain *specific phosphorylation* on a serine by a "Cdk5" polypeptide.

*The amount of direction provided by the inventor and The existence of working examples:* The specification discloses a single working example of the claimed method, i.e., the method set forth at pp. 15-18 of the specification, which appears to suggest that a single amino acid of SEQ ID NO:4 is *specifically phosphorylated* by Cdk, which is sufficient to enable a method for detecting Cdk5 serine kinase activity by contacting Cdk5 with the Dab1 of SEQ ID NO:4 or 5, determining whether serine at position 491 of SEQ ID NO:4 or 5 is or is not phosphorylated, wherein phosphorylation of serine at position 491 indicates Cdk5 activity. Other than this single working example, the specification fails to provide guidance as to whether other Dab1 polypeptides, including mutants and variants of SEQ ID NO:4 and 5, will have the ability to be *specifically phosphorylated* – and the serines that are *specifically phosphorylated* – by any polypeptide that is considered to be a "Cdk5" as encompassed by the specification's definition. The specification fails to provide guidance for using all methods that detect activity of any "Cdk5 serine kinase activity," including, e.g., Cdc2 activity, as broadly encompassed by the claims.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of isolating or generating variants of a polypeptide were known in the art at the time of the invention, it was not routine in the art to screen for all Dab1 polypeptides as encompassed by the claims, having a substantial number of modifications for those that have the desired activity/utility. Further, it was not routine to determine which of those “protein[s] with serine/threonine kinase activity that [are] structurally homologous to the mitotic cyclin dependent kinases” other than Cdk5 was able to phosphorylate a “Dab1” polypeptide and determine a use – if any – for such method.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of required experimentation, it is

the examiner’s position that undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable

correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired

biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

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**RESPONSE TO ARGUMENT:** Beginning at p. 8 of the Appeal Brief filed on 1/18/07, applicant argues the examiner has provided no scientific rationale or evidence to support the assertion that the disclosed Cdk5/Dab1 relationship is peculiar to a particular single species and thus the examiner has failed to establish a *prima facie* case of non-enabling disclosure. Applicant argues the "enabling nature" has been explained by providing a working example showing Cdk5 phosphorylation of serine 491 of mouse Dab1 and a sequence alignment of Dab1 from mouse, rat, and human and the structural relation between Dab1 from mouse and rat, human, dog, bird, cow, or zebrafish. According to applicant, in view of the teachings of the disclosure, a skilled artisan would be able to apply the method to Dab1 from other organisms.

Initially, it is noted that applicant's argument (beginning at p. 8) addresses species being representative of a genus, suggesting the argument is intended to address the issue of written description. However, the actual arguments appear to instead address the issue of enablement and have been treated by the examiner as such. In future correspondence, in order to avoid confusion as to what issue or rejection applicant is intending to address, applicant is requested to note the specific rejection that is being traversed.

Regarding the merits of applicant's argument, it is noted that applicant's argument is not found persuasive. While the examiner does not dispute applicant's evidence, it is noted that the claims are not limited to those Cdk5 or Dab1 polypeptides that are naturally occurring. As such, applicant's evidence is insufficient to establish an enabling disclosure for the *full scope* of the claimed

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invention, which broadly encompasses measuring the activity of any “protein with serine/threonine kinase activity that is structurally homologous to the mitotic cyclin dependent kinases” using SEQ ID NO:4 or 5 or any other “intracellular adapter protein that is phosphorylated by Cdk5 activity and by reelin tyrosine kinase activity” as broadly encompassed by the claims. For at least the reasons noted above, the specification fails to enable the full scope of the claimed invention.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

[12] Claims 1, 6-8, 15, 36-37, and 39-40 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Homayouni et al. (*J. Neurosci.* 19:7507-7515, 1999; cited as reference AE2 in the IDS filed on 3/25/02) as evidenced by Patrick et al. (*J. Biol. Chem.* 273:24057-24064, 1998). See MPEP 2112.III regarding a rejection under 35 U.S.C. 102/103. See also MPEP 2131.01 regarding a multiple reference 35 U.S.C. 102 rejection.

The claims are drawn to methods of detecting Cdk5 serine kinase activity in a biological sample, by determining whether Dab1 is phosphorylated on a serine residue.

The reference of Homayouni et al. teaches a method for phosphoamino acid analysis of mouse Dab1 recombinantly expressed in COS7 cells transiently transfected an expression vector encoding full-length mouse Dab1 fused to an HA epitope tag (p. 7508, column 2, p. 7511, column 1 and Figure 5). According to the method of Homayouni et al., the mouse Dab1 was immunoprecipitated with an anti-HA antibody and subjected to phosphoamino acid analysis, wherein the mouse Dab1 polypeptide is shown to have phosphoserine. This anticipates claims 1, 6-8, 15, 36-37, and 39-40 as written.

The following comments are provided to clarify the instant rejection. Although Homayouni et al. is silent as to the presence of enzymatically active Cdk5 in COS7 cells, the evidentiary reference of Patrick et al. (*J. Biol. Chem.* 273:24057-24064, 1998) discloses that COS7 cells exhibit endogenous catalytically active Cdk5 (p. 24061, column 2) and because enzymatically active Cdk5 is endogenously expressed in COS7 cells, the endogenous Cdk5 would have phosphorylated the recombinantly expressed Dab1 of Homayouni et al. While Homayouni et al. does not specifically teach detection of mouse Dab1 phosphorylation at serine 491 or 515, because Cdk5 is endogenously expressed in COS7 cells, the mouse Dab1 expressed in COS7 cells according to the method of Homayouni et al. would necessarily result in phosphorylation at serine 491 or 515, and thus at least one of the phosphoserines detected by the method

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of Homayouni et al. would have necessarily included phosphoserine at position 491 or 515 of mouse Dab1 (SEQ ID NO:4, encoded by GenBank 1771281). Even though COS7 cells are monkey cells and the Dab1 of the method of Homayouni et al. is mouse Dab1, according to applicant's remarks filed on 12/13/04 at p. 16, "[t]here is no reason to believe that Cdk5 from any source will not phosphorylate Dab1 on a preferred candidate sequence." While applicant may argue the reference of Homayouni et al. does not recognize Dab1 as being a substrate for phosphorylation by Cdk5, it is noted that according to MPEP 2112.I, "the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

For the reasons noted above, the examiner has presented a rationale tending to show inherency of the claimed invention. See MPEP 2112.IV and V. Since the Office does not have the facilities for examining and comparing applicant's method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e., that the mouse Dab1 phosphoserines detected by the method of Homayouni et al. do not include serine 491 or 515, and thus does not possess the same material structural and functional characteristics of the claimed method). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

***Examiner Comment/Clarification***

[13] Beginning at p. 5 of the Appeal Brief filed on 1/18/07, applicant argues the meanings of the terms "Cdk5" and "Dab1" are not unclear or indefinite. This argument responds in part to a rejection under 35 U.S.C. 112, second paragraph, which is no longer of record. To the extent applicant's arguments address the indefiniteness of the terms "Cdk5" and "Dab1" under 35 U.S.C. 112, second paragraph, the arguments will not be addressed as the terms, while being broad in scope, are not deemed to be indefinite.

The specification defines "Cdk5" as "a protein with serine/threonine kinase activity that is structurally homologous to the mitotic cyclin dependent kinases" (specification at p. 4, lines 14-15) and clearly defines "Dab1" as "an intracellular adapter protein that is phosphorylated by Cdk5 activity and by reelin tyrosine kinase activity" (specification at p. 4, lines 22-23). According to MPEP 2173.04, "[b]readth of a claim is not to be equated with indefiniteness...Undue breadth of the claim may be addressed under different statutory provisions, depending on the reasons for concluding that the claim is too broad...If the claim is too broad because it is not supported by the original description or by an enabling disclosure, a rejection under 35 U.S.C. 112, first paragraph, would be appropriate."

***Conclusion***

[14] Status of the claims:

Claims 1, 4-8, 10-11, 13-15, 32, and 35-40 are pending.

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Claims 1, 4-8, 10-11, 13-15, 32, and 35-40 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



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Art Unit 1656